JACC: HEART FAILURE VOL. 9, NO. 12, 2021
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STATE-OF-THE-ART REVIEW

Chloride in Heart Failure

The Neglected Electrolyte

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HIGHLIGHTS

- Despite the long-standing focus of guidelines/clinicians on sodium's role in HF, chloride is recently shown to have a more prominent contribution to the pathophysiology and prognosis of HF.
- Hypochloremia (low serum chloride level) is an independent predictor of adverse outcomes in acute or chronic HF.
- Various HF therapies may cause hypochloremia, and hypochloremia itself can initiate and exacerbate diuretic resistance in HF.
- Chloride abnormalities may be managed through a number of medical therapies.

ABSTRACT

The increasing burden of heart failure (HF) and emerging knowledge regarding chloride as a prognostic marker in HF have increased the interest in the pathophysiology and interactions of chloride abnormalities with HF-related factors and treatments. Chloride is among the major electrolytes that play a unique role in fluid homeostasis and is associated with cardiorenal and neurohormonal systems. This review elucidates the role of chloride in the pathophysiology of HF, evaluates the effects of treatment on chloride (eg, diuretic agents cause higher urinary chloride excretion and consequently serum hypochloremia), and discusses recent evidence for the association between chloride levels and mortality. (J Am Coll Cardiol HF 2021;9:904–915) © 2021 by the American College of Cardiology Foundation.

Heart failure (HF) is a highly prevalent disease with a substantial risk of morbidity and mortality worldwide (1). It is a prominent and growing health problem, with a 5-year mortality rate of ~50% after diagnosis. Electrolyte imbalances, especially potassium and sodium, are of interest in the clinical course of HF because their alterations may require intervention or adaptation

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 15, 2021; revised manuscript received July 22, 2021, accepted July 22, 2021.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2021.07.006

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of HF therapies and they appear to be associated with prognosis (2). In the last several decades, practice guidelines and clinicians predominantly focused on sodium, given its role in preserving fluid homeostasis and influence on progression of HF. However, sodium's often unnoticed counterion in salt, chloride, was recently discovered to also play an important role in the pathophysiology of HF and to be associated with neurohormonal system activity (3,4), replacing the long-standing view that it merely balances the other components of the metabolic profile.

Chloride and sodium are both major potent ions in extracellular fluid. A multitude of studies have purported the serum sodium abnormalities to be a predictor of poorer outcomes in patients with acute or chronic HF, but almost no studies have accounted for chloride levels in their analyses (Supplemental Table 1). Chloride has been shown to be a stronger predictor of outcomes than sodium in HF, and the existing controversy about the favorable versus detrimental effects of salt restriction in patients with HF may be related, in part, to its effect on chloride homeostasis. Changes in the plasma volume, vasopressin secretion, and renin-angiotensin-aldosterone (RAAS) systems that occur under worsening HF are purported to be primarily mediated by serum chloride, not by serum sodium levels (5). Also, several studies in patients with worsening HF have reported serum chloride to be inversely associated with mortality independent of serum sodium levels, and hence they have suggested its potential use as a prognostic marker in HF (6,7).

Although some evidence has emerged from these studies, many questions remain unanswered. Can chloride be used as a prognostic factor for HF? If so, what is the underlying pathogenesis that links chloride levels with outcomes? How does it interplay with sodium homeostasis in patients with HF? What HF-related factors (eg, pathophysiology, treatments) can affect the plasma chloride levels? Can chloride abnormality affect the patient's response to HF therapies? This review will examine existing evidence on chloride and its role in HF.

POSSIBLE ROLE OF CHLORIDE IN HF PATHOPHYSIOLOGY

Chloride is frequently tested in patients with HF and although there is no universal consensus on the normal chloride level ranges, hypochloremia and hyperchloremia are often defined as <96 mmol/L and >105 mmol/L, respectively (6).

Electrolytes are important for signaling in the heart and contribute to cellular excitability in the cardiovascular system. Activation of cardiac chloride channels affects the membrane potential and action potential duration in the sino-atrial node, which can result in arrhythmias (8). This arrhythmogenesis resulted from abnormal chloride levels, which are partly mediated by the dysregulated myocyte intracellular pH and K^+ levels, and can lead to sudden cardiac death (6). Patients with HF have shown a 50% decline in the presence of chloride transfer regulator called the cystic fibrosis transmembrane conductance regulator in an adaptive mechanism during the HF progression (8). Consequently, this may lead to an instability of repolarization and a higher tendency to arrhythmias. Moreover, this electrolyte imbalance can cause dysregulation of myocyte intracellular pH, which is shown to be an arrhythmogenic factor (6). The above-mentioned adaptive remodeling of chloride channels can contribute to the progression of myocardial hypertrophy and subsequent HF (8).

More importantly, chloride is well known to play an important role in fluid homeostasis, neurohormonal activation, and diuretic resistance (3,9), which are generally recognized as major factors in the development and progression of HF. These factors will be discussed in greater detail in this review.

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

RAAS = renin-angiotensin-aldosterone system

WNK = with-no-lysine protein kinases

THE EXISTING PUBLISHED DATA ON CHLORIDE ABNORMALITIES IN HF

Sixteen studies have shown that low serum chloride level is associated with adverse outcomes (**Table 1**) in patients who are hospitalized with acute HF (6,787 patients) (1,7,10-16) as well as in outpatients with chronic HF (18,757 patients) (6,9,10,17-20).

A few studies suggested that both hypochloremia and hyperchloremia were associated with adverse outcomes in a U-shaped correlation (6,10,19,20). Others either did not study hyperchloremia (9,13-17,21) or studied it but did not find a correlation between hyperchloremia and adverse outcomes (7,11,12,18).

In some studies, serial measurements, instead of a single measurement, were used to see whether a change in chloride concentration was related to the outcome of interest. Kataoka (17) looked at the change of chloride levels in patients with HF and reported an increase in chloride concentration during worsening HF, which was decreased after HF

TABLE 1 Studies Exploring the Link Between Chloride Abnormalities and Outcome in Patients With HF

First Author, Year, Country (Ref. #)	Design	Participants	N	Single or Serial Measurement	Dichotomous/ Continuous (Cutoff)	Primary Endpoint	Key Findings
Cuthbert et al, 2018, United Kingdom (6)	Registry-based cohort	Outpatients with HF	4,705	Single	Categorical and continuous Hypochloremia: <96 mmol/L Hyperchloremia: >105 mmol/L	All-cause mortality, composite endpoint of mortality/HFH	Every unit decrease in chloride was associated with 4% and 3% increase in death alone and composite of death/ HFH, respectively. Lowest quartile associated with 2-fold increased risk of mortality.
Ferreira et al, 2017, France (10)	EPHESUS and CAPRICORN RCT	In- or outpatients, post-AMI (HFrEF)	7,195	Single	Continuous (tertiles)	All-cause mortality, CV mortality, and HFH	Chloride levels <100 mmol/L were associated with higher risk of mortality, but not HFH, in the context of sodium ≤138 but not in sodium >141 mmol/L.
Grodin et al, 2015, USA (7)	Population-based cohort	Hospitalized patients with AHF	Main cohort: 1,318 Validation cohort: 876	Serial (admission and discharge)	Categorical and continuous (tertiles) Hypochloremia: <96 mmol/L	All-cause mortality	Chloride <96 mmol/L associated with higher mortality. Mortality of <1 y decreased by 6% for every unit increase in admission chloride level. Similar findings in validation cohort.
Grodin et al, 2016, USA (12)	Registry-based cohort	Outpatients with HF	1,664	Single	Continuous (quartiles)	5-y all-cause mortality	For each 4.1-mmol/L decrease in serum chloride concentration, 5-y all-cause mortality risk increased by 29%.
Grodin et al, 2017, USA (11)	ROSE-AHF RCT	Hospitalized patients with AHF	358	Serial (at randomization and during hospital stay)	Continuous (tertiles)	Diuretic response, renal function at 72 h, death, and rehospitalization at 60 and 180 d	For each mmol/L increase in serum chloride, the risk of 60-d death, 60-d death/ rehospitalization, and 180-d death decreased with 14%, 10%, and 9%, respectively. Lower serum chloride levels at baseline were associated with less diuretic efficiency.
Grodin et al, 2018, USA (19)	TOPCAT RCT	Outpatients with HFpEF (LVEF ≥45)	942	Serial measurements, baseline used for evaluating association with outcomes	Continuous (tertiles) Hypochloremia: ≤96 mmol/L	Composite of CV death, HFH, or aborted cardiac arrest	5-y all-cause death and CV death increased with 29% and 51%, respectively, for each 4.05-mmol/L decrease in serum chloride level. No association with HFH.
Grodin et al, 2018, USA (18)	Registry-based cohort	Outpatients with HF	438	Single	Continuous (tertiles)	Composite endpoint of death, heart transplant, or LVAD placement	Each mmol/L reduction in chloride level was associated with 6% increase in composite endpoint, after adjustment for sodium and bicarbonate.
Hanberg et al, 2016, USA (9)	Registry-based cohort	Outpatients with HF	162	Single	Dichotomous Hypochloremia: ≤96 mmol/L	Diuretic efficiency, plasma renin activity, all-cause mortality	Hypochloremia was associated with reduced survival (HR: 5.7) and impaired diuretic efficiency (OR: 7.3).
Kataoka, 2018, Japan (17)	Registry-based cohort	Outpatients with HF	47	Serial		Change in chloride concentration	During HF therapy with conventional diuretics, the chloride changes were greater than the changes in sodium levels. Chloride levels increased during worsening HF.
Khan et al, 2015, USA (13)	Population-based cohort	Hospitalized patients with AHF	674	Serial (admission and discharge)	Dichotomous CDA: change in serum bicarbonate ≥3 mmol/L Non-CDA: change <3 mmol/L	In-hospital mortality and composite endpoint of 30-d all-cause mortality and HFH	In-hospital mortality was lower in the group with CDA (OR: 0.11). No difference in 30-d composite endpoint.

Continued on the next page

treatment with conventional diuretic agents. A few studies explored the effect of chloride change in hospital on clinical outcomes and the majority showed higher risk of mortality in those with either progressive or persistent hypochloremia during hospital stay (11,14,16).

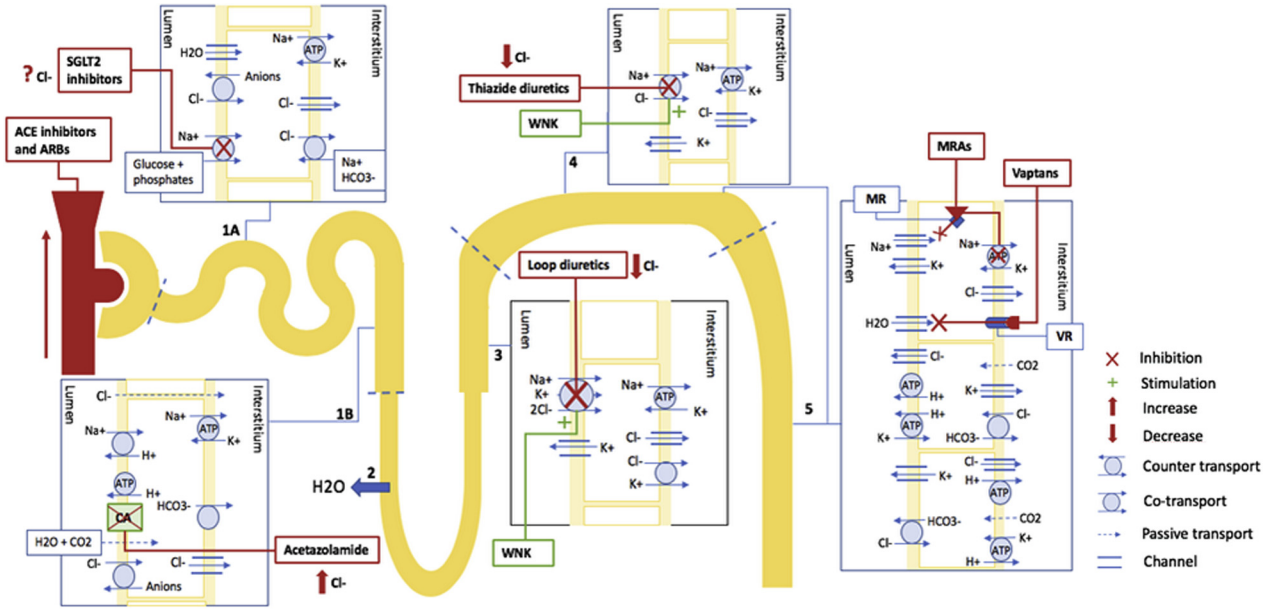
It is suggested that sodium and chloride should be assessed together in patients with decompensated

TABLE 1 Continued

First Author, Year, Country (Ref. #)	Design	Participants	N	Single or Serial Measurement	Dichotomous/ Continuous (Cutoff)	Primary Endpoint	Key Findings
Kondo et al, 2018, Japan (14)	Registry-based cohort	Hospitalized patients with AHF	208	Serial (admission and discharge)	Dichotomous and change Hypochloremia: <98 mmol/L	HF death, non-CV death, all-cause death	Lower admission and discharge chloride levels were associated with increased HF mortality. Persistent and progressive hypochloremia during hospitalization were associated with increased risk of HF death (HR: 9.13 and 4.65, respectively) and all-cause death (HR: 3.63 and 2.10, respectively) compared to the groups without hypochloremia.
Marchenko et al, 2020, USA (21)	Population-based cohort	Hospitalized patients with AHF	1,241	Serial (admission and discharge)	Dichotomous Hypochloremia: <96 mmol/L	30-d hospital readmission	Hypochloremia either on admission or discharge was independently associated with a higher 30-d rehospitalization rates (adjusted OR: 1.35), but only explained 4% of the variability of the rehospitalization outcome.
Radulovic et al, 2016, Croatia (15)	Registry-based cohort	Hospitalized patients with AHF	152	Single	Dichotomous Hypochloremia: <98 mmol/L	In-hospital and 3-mo mortality, hyponatremia at follow-up	Hypochloremia at admission was associated with higher in-hospital and 90-d death in univariate analysis, but not after adjustment for age, sodium and cholesterol levels, and statin therapy. Hypochloremia associated with higher risk of hyponatremia at 90 d (OR: 27.1)
Ter Maaten et al, 2016, the Netherlands (16)	PROTECT RCT	Hospitalized patients with AHF (HFrEF)	1,960	Serial (baseline, 7th and 14th d)	Continuous (quintile) Hypochloremia: <96 mmol/L	Diuretic responsiveness, decongestion, and 180-d all-cause mortality	With each unit decrease in serum chloride level, the risk of 180-d mortality increased in patients with hypochloremia by 4% and 7% at 7th and 14th d, respectively. Progressive and persistent hypochloremia within 2 wk from baseline were associated with higher mortality rates than those for patients who were nonhypochloremic (HR: 3.11).
Testani et al, 2016, USA (20)	BEST RCT	In- and outpatients with HF (HFrEF)	2,699	Serial (baseline, 3 and 12 mo)	Dichotomous Hypochloremia: ≤96 mmol/L	All-cause mortality	Low serum chloride independently associated with increased mortality. Each 4.5-mmol/L decrease in baseline serum chloride increased the adjusted mortality risk by 30%.
Zhang et al, 2018, China (1)	Registry-based cohort	Hospitalized patients with HF	905	Single	Continuous (quartiles)	All-cause death	8% higher adjusted risk of mortality for every unit decrease in serum chloride. Mortality risk increased for hypochloremia in the context of hyponatremia (HR: 4.30).

AHF = acute heart failure; AMI = acute myocardial infarction; BEST = Beta-Blocker Evaluation of Survival Trial; CAPRICORN = Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left-Ventricular Dysfunction; CDA = chloride depletion alkalosis; CV = cardiovascular; EPHESUS = Eplerone, a Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction; HF = heart failure; HFH = heart failure (re)hospitalization; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; OR = odds ratio; PROTECT = Placebo-controlled Randomized Study of the Selective A1 Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; RCT = randomized controlled trial; ROSE-AHF = Renal Optimization Strategies Evaluation in Acute Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial.

FIGURE 1 Renal Regulation of the Chloride Homeostasis



Sixty percent of chloride is reabsorbed in the proximal convoluted tubule. In step **1A**, sodium, bicarbonate, and other nonchloride anions are reabsorbed. In step **1B**, most of the secreted Cl^- is reabsorbed passively through the concentration gradient generated by step **1A**, and carbon anhydrase increases serum HCO_3 levels. In step **2**, there is only passive water transport, whereas the thick ascending limb (step **3**) is impermeable for water and the sodium-potassium-2 chloride (Na-K-2Cl) cotransporter is active. In step **4**, sodium and chloride are reabsorbed via the sodium-chloride cotransporter. The basolateral Na-K-adenosine triphosphatase (ATPase) pump creates a low sodium gradient, so direct coupled sodium/chloride transport can be facilitated. Chloride is passively and indirectly reabsorbed in this step, because of the negative potential caused by the transport of sodium via the apical epithelial sodium channels. Serine-threonine kinases (with-no-lysine protein kinases [WNKs]) play an important role as chloride sensors and are in control of Na^+-K^+-$2Cl^-$ and Na^+-Cl^- cotransporters. In step **5**, the final urinary chloride concentration is regulated via paracellular transport. If chloride is low on the serum electrolyte balance, there will be maximal reabsorption in the collecting duct to conserve normal chloride levels. ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blocker; CA = carbon anhydrase; MR = mineralocorticoid receptor; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter 2; VR = vasopressin receptor 2 antagonists.

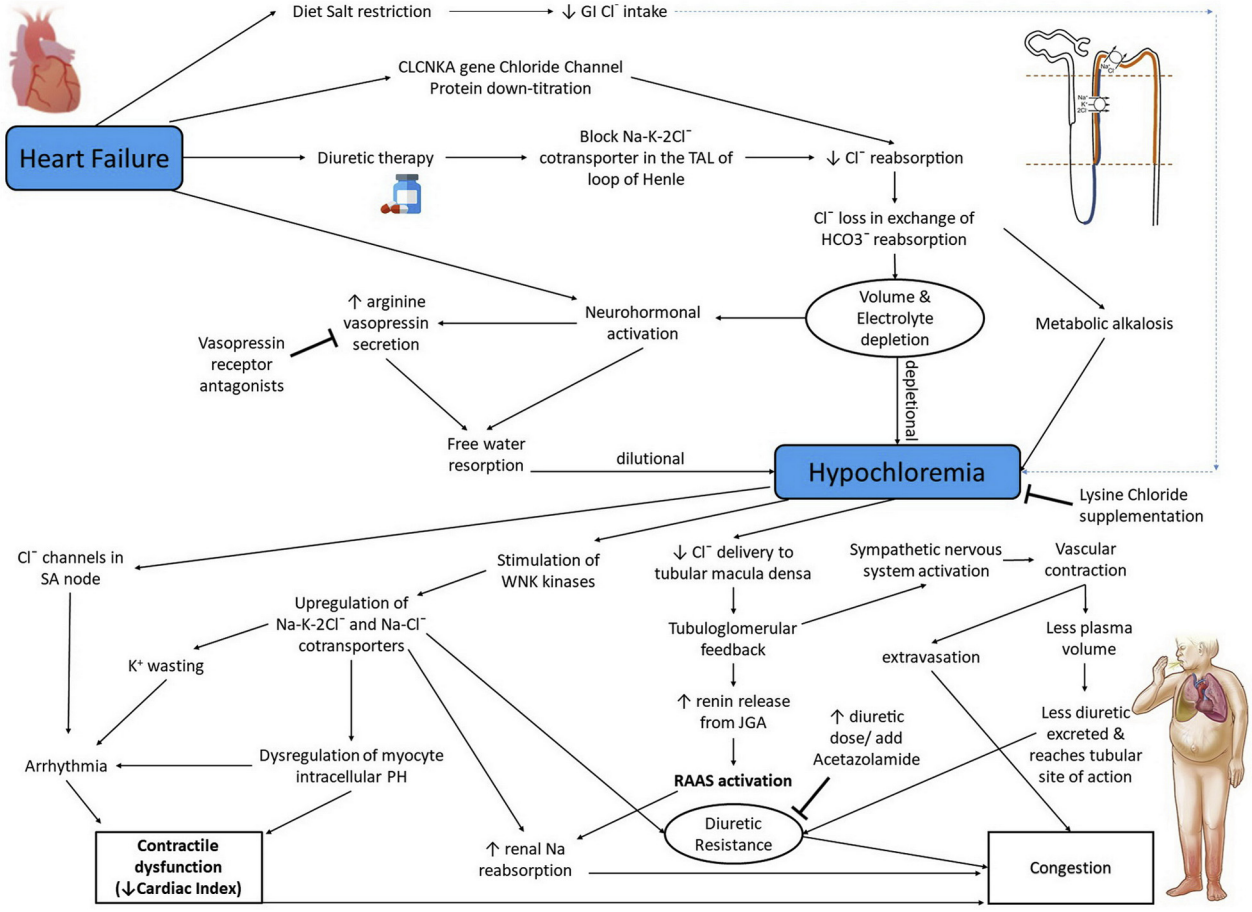
HF. The majority of studies (1,6,7,10,17), but not all (16), have reported a correlation between chloride and sodium, although the observed correlation was very modest in 2 studies (9,20). Some studies showed a link between hypochloremia and mortality in the context of hyponatremia, but the association attenuated at higher sodium levels (1,10). Whether sodium or chloride have any effect on clinical outcomes independent of each other remains uncertain and requires further research. Although studies suggested a link between hyponatremia and clinical outcomes in the univariate analysis, this link often disappeared with adjustment for covariates including chloride level (6,7,9,12,14,16,20,21).

The changes in chloride concentration were shown to be relatively greater than the changes in sodium concentration in 1 (17) of 3 studies (14,16,17) reporting the change of both electrolytes during the course of treatment. The risk of adverse outcomes is shown to be increased in higher baseline sodium/chloride ratios (1).

POTENTIAL MECHANISMS OF THE EFFECT OF CHLORIDE LEVEL IN HF

CHLORIDE AND THE GASTROINTESTINAL TRACT. Prominent causes of hypochloremia are related to the loss of chloride anions in the gastrointestinal tract or kidneys. Dietary intake, intestinal absorption, and excretion are important aspects that need to be considered in the gastrointestinal tract. Adequate intake of chloride is set at a level equivalent to the molar basis of sodium, because almost all dietary chloride comes with sodium and thus deficiencies are rare, except in the context of salt restriction (22). On a daily basis, the gastrointestinal tract is responsible for handling 8 to 10 L of fluid containing 800 mmol of sodium and 700 mmol of chloride. Salivary gland

FIGURE 2 **Pathophysiological Relations Between HF and Hypochloremia**



The upper half of this schematic figure depicts the mechanisms with which heart failure (HF) could lead to hypochloremia and the lower half covers the pathways that connect hypochloremia with contractile dysfunction and heart failure decompensation. GI = gastrointestinal; JGA = juxtaglomerular apparatus; RAAS = renin-angiotensin-aldosterone system; SA = sinoatrial; TAL = thick ascending limb of the loop of Henle; WNK = with-no-lysine protein kinases.

acinar cells secrete chloride and sodium as an isotonic fluid. Parietal cells secrete HCl in response to the release of gastrin caused by the presence of peptides (ie, meal) in the gastric lumen. About 98% of the chloride intake will be absorbed (22). There are 3 distinct mechanisms responsible for chloride absorption from the intestinal lumen. The main pathway is the electroneutral coupled Na/H and Cl/HCO_3 exchange, which results in Na^+ and Cl^- absorption in exchange for H^+ and HCO_{3-} excretion. The other 2 mechanisms are paracellular pathway and bicarbonate-dependent chloride absorption. Intestinal absorption can be impaired in HF through the congestion of the splanchnic circulation and the subsequent intestinal wall edema and barrier dysfunction (23). Eventually, only 100 mL fluid is lost through the stools per day and this contains 10 to 15 mmol/L chloride, which can exceed 90 mmol/L in case of malabsorption.

CHLORIDE AND THE KIDNEY. Kidney has a central role in the body's electrolyte homeostasis. The urinary concentration of chloride is regulated by the amount of chloride filtered by the glomeruli and the balance of resorption and secretion along the nephron (**Figure 1**) and normally ranges between 110 and 250 mmol/L. In the general population, the amount of excreted urinary chloride roughly equals the intake. However, renal dysfunction is prevalent in patients with HF and related to a worse prognosis. In patients with HF, renal blood flow is often impaired because of a decrease in cardiac output and an increase in central venous congestion. Chloride is the

main modulator of the tubuloglomerular feedback in the kidney, and hypochloremia in HF would interfere with the kidney's regulatory role in electrolyte homeostasis and diuresis.

CHLORIDE AND NEUROHORMONAL ACTIVATION. Chloride has a unique role in homeostasis that is distinct from sodium. As demonstrated in **Figure 2**, hypochloremia leads to decreased chloride delivery to the macula densa in nephrons, resulting in an increase in the secretion of renin from the juxtaglomerular apparatus caused by tubuloglomerular feedback in the kidney (3). This salt-sensing and physiological feedback is dependent on chloride rather than sodium (9). There is also activation of the sympathetic nervous system, which particularly results in renal afferent vasoconstriction causing a decrease in renal blood flow and therefore less natriuresis and diuresis, leading to more congestion. Serine-threonine kinases (with-no-lysine protein kinases [WNK]) play an important role as chloride sensors for changes in intracellular chloride concentration, cell volume, and extracellular osmolarity. Lower serum chloride activates a cascade, in which the WNK family increases the activity of Na-K-2Cl^- cotransporter in the thick ascending limb of the loop of Henle, as well as the Na-Cl^- symporters in the distal convoluted tubule to facilitate the chloride reabsorption (3). Up-regulation of these transporters can lead to potassium wastage and arrhythmias (8). Changes in plasma potassium can affect the Na-Cl^- symporter because they alter the intracellular chloride concentration and thereby modulate WNK activity. When plasma potassium is high and consequently aldosterone is secreted, the WNK activity is inhibited (24). Recent studies show that chloride appears to bind directly to a catalytic site of WNK, phosphorylating sodium regulatory pathways, and thereby regulating blood pressure and electrolyte homeostasis (20). This represents a plausible mechanistic link between HF pathology and chloride imbalances (9).

Neurohormonal activation is modulated by the HF medications, ventricular dysfunction, and renal dysfunction (25). Maladaptive neurohormonal activation and acid-base changes during the chronic HF progression can affect the serum chloride concentration by activating the neural thirst center and impairing the vasopressin secretion (1). According to the "chloride theory," changes in serum chloride levels are the primary determinants of changes in RAAS and plasma volume (26). For example, total renin levels were shown to be higher in patients with hypochloremia than in patients without hypochloremia, and this inverse correlation remained significant even after adjustment for serum sodium (9). The B-type natriuretic peptide (BNP) is secreted by ventricular myocytes caused by elevated ventricular filling pressure, and it counteracts the effects of RAAS and sympathetic activity. Chloride and BNP both seem to be predictors of outcome in HF, but it is unclear how and whether BNP modulates the prognostic value of chloride. In a United Kingdom study, hypochloremia was associated with adverse outcome independent of BNP (6). In the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial, after adjustment for clinical covariates including natriuretic peptides, there was a 12% decrease in the risk of cardiovascular death and HF hospitalization per each 5 mmol/L increase in serum chloride level (27).

ACID BASE IMBALANCES. The interdependence among serum chloride, sodium, potassium, and bicarbonate is shown in the anion gap formula: Anion Gap $= S_{Na} + S_K - S_{HCO3^-} - S_{Cl}$. This equation highlights why hypochloremia occurs frequently with metabolic alkalosis. These 2 combined are called "chloride depletion alkalosis," which is a state of volume contraction in the extracellular fluid caused mainly by diuretic-induced natriuresis and diuresis. In laboratory results, this can be seen as a rise in pH and serum bicarbonate level, as well as low serum chloride concentrations. The exact role of pH as prognostication marker has not been fully explored, but pH has been shown to be affected by chloride level in the forms of chloride depletion alkalosis or hyperchloremic metabolic acidosis (3). Chloride depletion alkalosis is shown to be an independent predictor of in-hospital mortality in patients with decompensated HF (13). In HF, electrolyte depletion occurs mostly as a result of salt restriction and loop and thiazide diuretic therapy and metabolic alkalosis is often seen as a consequence of diuretic usage (28).

HYPERCHLOREMIA. As mentioned, several studies suggested a U-shaped correlation between serum chloride levels and adverse outcomes in patients with HF (6,10,19,20). Hyperchloremia occurs when the plasma concentration of chloride is elevated in excess of 105 to 115 mmol/L; although, there is no universal definition and the criteria may differ between laboratories. Mechanisms leading to hyperchloremia include excessive electrolyte-free or hypotonic fluid loss and disproportionate chloride administration (eg, excessive intravenous saline administration). Hyperchloremia is distinct from hyperchloremic metabolic acidosis where elevated serum chloride is accompanied by a decrease in serum bicarbonate

concentration and a drop in blood pH. Hyperchloremic metabolic acidosis can be of renal or extrarenal origin. Proximal or distal renal tubular acidosis should be considered when a patient presents with hyperchloremic metabolic acidosis. In proximal renal tubular acidosis, the filtered bicarbonate is lost by kidney wasting (29). This will lead to the reabsorption of chloride by the kidney for maintaining volume. In distal renal tubular acidosis, there is insufficient bicarbonate production/regeneration in the kidneys to compensate and buffer for the endogenous acid (29). Secretory diarrhea is the common extrarenal cause of hyperchloremic metabolic acidosis that stimulates chloride resorption in exchange of bicarbonate secreted into the intestinal lumen with diarrhea.

HFrEF AND HFpEF. As shown in **Table 1**, only 3 studies enrolled only patients with heart failure with reduced ejection fraction (HFrEF), 1 included only patients with heart failure with preserved ejection fraction (HFpEF), and the others represented a mix consisting mainly of patients with HFrEF. Whether the role of chloride is similar for the 2 HF phenotypes remains unknown (30); although, at least 1 study demonstrated that hypochloremia was more common in HFrEF (6).

COMORBIDITIES. Patients with HF and hypochloremia were more likely to have diabetes mellitus than were patients with normal or higher chloride levels (6,10,18). In the study of Grodin et al (12), the association between hypochloremia and mortality was unchanged after adjustment for diabetes mellitus, chronic obstructive pulmonary disorder, and coronary artery disease. Low serum chloride is of prognostic value in both patients with chronic kidney disease (31) and those with hypertension (32). However, the question of whether patients with HF and certain comorbidities are more prone to hypochloremia remains to be investigated in future studies.

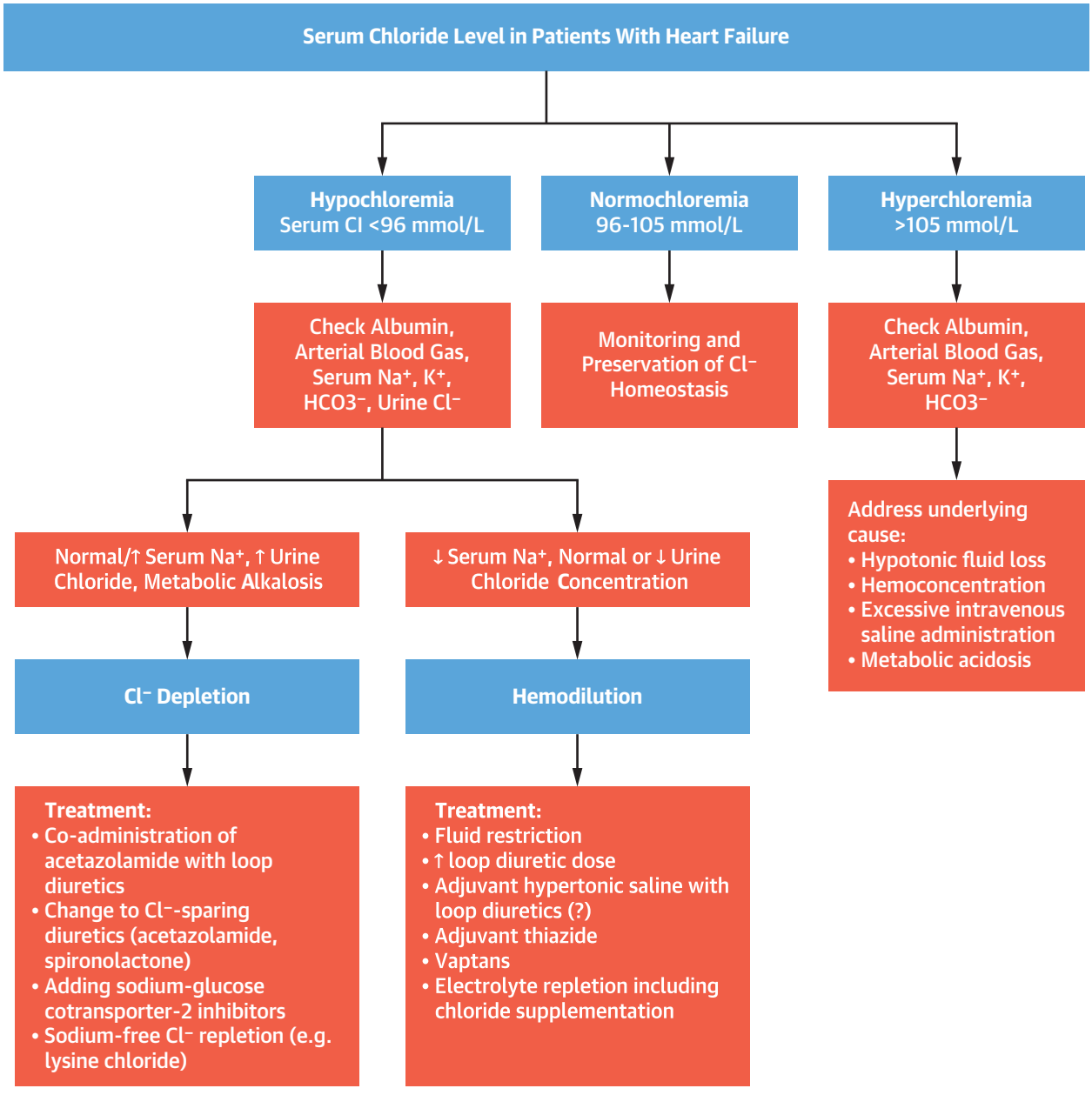
THE EFFECT OF HF THERAPY ON CHLORIDE LEVEL

SALT RESTRICTION. Serum electrolyte concentrations may be influenced by the amount of dietary sodium chloride (the most abundant dietary salt) intake (33). Despite limited evidence for the beneficial effect of sodium or fluid restriction in HF, the current HF guidelines endorse that strategy to minimize the risk of volume overload and for symptom improvement. However, recently attention has focused on potential detrimental effects from salt restriction, possibly caused by further neurohormonal activation and HF progression, which are caused by hypochloremia (20), hyponatremia, or both. The relationship between a low intake and low serum electrolyte concentrations remains unknown for patients with HF. Moreover the actual clinical impact of salt restriction is yet to be established in this patient population. This question is expected to be answered by the ongoing SODIUM-HF (Study of Dietary Intervention Under 100 MMOL in Heart Failure; NCT02012179) trial.

HF MEDICATIONS. Although there is no compelling evidence that diuretic agents improve survival in patients with HF, they are the first-line therapy to prevent and treat fluid overload and to improve symptoms, through renal sodium and chloride wasting. Diuretics may have differences in tubuloglomerular feedback response, with loop diuretic agents disrupting it whereas others do not. This phenomenon has implications for sodium and chloride handling and neurohormonal response. Inhibition of the Na-K-2Cl cotransporter results in less electrolyte reabsorption, which will lead to extravascular volume depletion and consequently neurohormonal activation. The latter leads to free water reabsorption and worsening of hypochloremia. Loop diuretic agents can increase chloride excretion by ~20-fold. Compared with sodium and potassium excretion, there is an extra 10% to 20% chloride loss with loop diuretic agents (20). As the affected pump (ie, Na-K-2Cl) is located in the thick ascending limb of the loop of Henle, further along the nephron there is still a possibility to reabsorb sodium, which prevents hyponatremia in diuretic therapy. More distally, there is minimal possibility to reabsorb chloride, hence we observe hypochloremia. Thiazides can cause both hyponatremia and hypochloremia through inhibiting the Na-Cl cotransporter in the distal convoluted tubule (10). Diuretic treatment in combination with salt restriction may limit tubular delivery and reabsorption of chloride even more and aggravate the hypochloremia (25). Not surprisingly, a higher diuretic use is reported among patients with the lowest quartile of serum chloride level (30).

Treatment with mineralocorticoid receptor antagonists may not ameliorate hypochloremia, but it can prevent further decline in serum chloride levels in patients with HF. Studies have shown no association between spironolactone and a decrease in serum chloride concentrations (19). The carbonic anhydrase inhibitor, acetazolamide, increases serum chloride

CENTRAL ILLUSTRATION **Management of Patients With Heart Failure Based on Their Serum Chloride Status**


Serum Chloride Level in Patients With Heart Failure
Hypochloremia
Serum Cl <96 mmol/L
Normochloremia
96-105 mmol/L
Hyperchloremia
>105 mmol/L
Check Albumin, Arterial Blood Gas, Serum Na+, K+, HCO3−, Urine Cl−
Monitoring and Preservation of Cl− Homeostasis
Check Albumin, Arterial Blood Gas, Serum Na+, K+, HCO3−
Normal/↑ Serum Na+, ↑ Urine Chloride, Metabolic Alkalosis
↓ Serum Na+, Normal or ↓ Urine Chloride Concentration
Address underlying cause:
• Hypotonic fluid loss
• Hemoconcentration
• Excessive intravenous saline administration
• Metabolic acidosis
Cl− Depletion
Hemodilution
Treatment:
• Co-administration of acetazolamide with loop diuretics
• Change to Cl−-sparing diuretics (acetazolamide, spironolactone)
• Adding sodium-glucose cotransporter-2 inhibitors
• Sodium-free Cl− repletion (e.g. lysine chloride)
Treatment:
• Fluid restriction
• ↑ loop diuretic dose
• Adjuvant hypertonic saline with loop diuretics (?)
• Adjuvant thiazide
• Vaptans
• Electrolyte repletion including chloride supplementation

Zandijk, A.J.L. et al. J Am Coll Cardiol HF. 2021;9(12):904–915.

This algorithm depicts the several key parameters used in the assessment of patients with heart failure with regard to their serum chloride status, various phenotypes involved, and the suggested therapeutic approaches for each phenotype.

levels and decreases HCO_3^- independently of sodium, through inhibition of the intracellular and luminal carbonic anhydrase in the proximal tubule (3).

No studies have explored the effect of treatment with angiotensin receptor blockers, angiotensin converting enzyme inhibitors, or beta-blockers on chloride homeostasis. Hyperkalemia is the only electrolyte disturbance that is widely reported with angiotensin receptor blocker and angiotensin converting enzyme inhibitor therapies.

THE EFFECT OF CHLORIDE ABNORMALITY ON RESPONSE TO HF TREATMENTS

DIURETIC RESISTANCE. Adaptive renal mechanisms to maintain volume status may be initiated by chloride depletion and may eventually lead to diuretic resistance (9,11). A significant association was shown between chloride and diuretic response, even after adjustment for sodium and bicarbonate levels (16). The reduced quantity of diuretic reaching the tubular site of action and an inadequate tubular response to the delivered diuretic could explain the reduced diuretic efficiency. Also, as mentioned, a family of chloride-sensitive kinases known as WNK were recently identified to have a vital role in regulating Na-K-2Cl^- cotransporters in the thick ascending limb of the loop of Henle and the Na-Cl^- symporters in the distal convoluted tubule on which loop and thiazide diuretic agents operate. Hypochloremia activates these transporters to reabsorb chloride, unlike loop and thiazide diuretic agents that work by inhibiting these transporters. These opposing effects link hypochloremia to diuretic resistance. A change of diuretic drug (switching from a loop to a nonloop diuretic), a dose increase, or alternatively, chloride supplementation are some measures suggested for overcoming diuretic resistance (9,11). It is noteworthy that the above-mentioned loop diuretic dose increase that occurs frequently in current practice to address the diuretic resistance induces even lower serum chloride levels and possibly creates a vicious cycle (9).

DILUTION AND DEPLETION. Patients with HF seem to have 2 distinct biochemical profiles. In patients with HF, a greater relative wasting of chloride versus sodium can suggest that depletion rather than dilution is the underlying mechanism (9). Even though the urinary chloride concentrations can be used to differentiate between depletion and dilution phenotypes, these are less frequently tested (6,11).

The fraction of serum chloride versus sodium can be used to distinguish these 2 phenotypes. In the first patient group, with both hypochloremia and hyponatremia, hemodilution appears to be the main contributor (6) with limited tubular chloride resorption, higher arginine vasopressin secretion, and overstimulation of vasopressin receptor 2, which results in increased water retention by the kidneys (**Figure 2**) (12,25). Whereas increasing the dose of loop diuretic may be appropriate to treat a patient with severe congestion and hemodilution, it may worsen hypochloremia (11). This patient group can be treated with fluid restriction and electrolyte supplementation (28), as well as with mineralocorticoid receptor antagonists that can counteract the potassium loss that is observed in these patients (33).

The second phenotype are patients with hypochloremia and normal sodium levels, which may be caused by chloride depletion as a consequence of diuretic therapy (6). A metabolic alkalosis is often present, which can be treated with aggressive potassium and chloride repletion.

CURRENT THERAPIES FOR HYPOCHLOREMIA. Hypochloremia can be a consequence of salt and water handling along the nephron in patients with HF. Some studies have explored possible therapies for hypochloremia, which are summarized in the **Central Illustration**. A change of the diuretic regimen might be an option. In a post hoc analysis from the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial; NCT00094302) lower serum chloride levels were not associated with spironolactone use, in contrast to treatment with loop diuretic agents (19). Another study reported that coadministration of acetazolamide with loop diuretic agents can reduce the chloride loss by approximately 5%. More insights on the efficacy of the combined therapy with acetazolamide and loop diuretic agents in patients with HF are expected to be provided through the ongoing ADVOR (Acetazolamide in Decompensated Heart Failure With Volume Overload; NCT03505788) trial. Administration of adjuvant thiazides may theoretically reduce chloride wastage (20).

Manipulation of the serum chloride concentration could become an attractive novel therapeutic target for HF treatment (33). Therapies may directly or indirectly affect serum chloride level. Recently, there have been small studies on newer agents, sometimes with conflicting results. Sodium glucose cotransporter 2 inhibitors seem to maintain or increase serum levels of chloride, without any change in serum Na and K levels, but with a decrease in HCO_3 concentrations (34). This effect on serum chloride levels may be mediated in early treatment stages by RAAS activation caused by vessel contraction, and decreased blood pressure resulted from osmotic diuresis in sodium glucose cotransporter 2 inhibitor treatment, inhibition of $NaHCO_3$ reabsorption caused by the buffering effect of increased organic acid metabolites such as ketone bodies, and inhibition of Na-H exchanger 3 in the proximal convoluted tubule (34). Vasopressin receptor 2 antagonists ("vaptans") increase free water clearance by antagonizing the vasopressin receptors 2 and result in improvement of hyponatremia and presumably low serum chloride levels (25). The use of

vaptans would be expected to change sodium and chloride equally in a 1:1 molar ratio in a hemodilution state (20), meaning that they have potentially equal ameliorating effects on hyponatremia and hypochloremia. Hypertonic saline may be a possible treatment intervention in acute decompensated HF, as this was shown to improve serum chloride abnormalities (35), but this requires further testing in adequately powered and well-designed randomized controlled trials.

Supplementation of lysine chloride directly increases chloride levels approximately by 2.2 to 2.3 mmol/L, but its longer-term pharmacological impact is not fully investigated yet (25). Hence, a randomized controlled trial is underway (expected completion: March 2023) on the effects of sodium-free chloride supplementation in patients with decompensated HF concomitantly treated with intravenous diuretic agents (Mechanism and Effects of Manipulating Chloride Homeostasis in Stable Heart Failure [NCT03440970]).

FUTURE DIRECTIONS

Emerging evidence indicates that chloride is a prognostic factor for HF outcomes, but it is not yet a therapeutic target. In patients with HF, the presence of hypochloremia may indicate a more generalized disturbance of cardiorenal homeostasis, in opposition to an isolated low serum sodium level (19). In the **Central Illustration**, we suggested a management algorithm based on the existing data for patients with HF and different serum chloride levels, but there is a significant knowledge gap that needs to be addressed in future studies. For instance, whether the role of chloride is similar for the 2 HF subtypes remains unknown and requires further investigation (30). The prognostic impact of chloride levels might differ between the normal and pathological conditions. The prognostic effect of serum chloride abnormalities in HF might be more striking in the presence of certain comorbidities such as chronic kidney disease, given its critical importance in HF and the kidney's role in electrolyte homeostasis.

Advice on routine monitoring of chloride concentration through testing blood and urine samples and preservation of chloride homeostasis in patients with HF could be useful in clinical practice especially in the future if interventions either targeting it or relating to it are proved useful. Sodium restriction and diuretic therapy might result in hypochloremia (25), which is shown to be associated with worsening HF and poorer survival (20). Patients with HF who have a lower urinary chloride concentration may benefit from the down-titration of loop diuretics; however, all previous studies exploring that have been underpowered. Targeting WNKs may be a potential therapeutic option in HF, as inhibition of WNK can decrease the activity of Na-K-2Cl$^-$ and Na-Cl$^-$symporter. This could be more effective than targeting one of the cotransporters directly. Serial measurements can identify patients who are rapidly deteriorating and at risk for adverse outcomes and may provide insight on need for treatment alterations (14,16).

Prospective studies, preferably randomized clinical trials with large numbers of patients are required to evaluate the effect of serum chloride manipulation as a prognostic factor in patients with HF. The prognostic value of serum chloride and its interaction with other electrolytes such as sodium in HF remains to be fully delineated and harnessed as a potential therapeutic target.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Canadian VIGOUR Centre provided in-kind support via data management and statistical analysis. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS chloride, heart failure, hypochloremia, outcome, pathophysiology, prognosis, treatment

APPENDIX For a supplemental table and references, please see the online version of this paper.

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